

# DRUG DISCOVERY

## FDA approved drugs – February 2013

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Received 17 February; accepted 11 March; published online 01 April; printed 16 April 2013

### 1. STIVARGA (REGORAFENIB)

#### 1.1. Company

Bayer Healthcare Pharmaceuticals; Approved by February 2013

#### 1.2. Treatment Area

Gastrointestinal stromal tumor

#### 1.3. General Information

Stivarga (regorafenib) is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. It is specifically indicated for patients with locally advanced, metastatic gastrointestinal stromal tumor who have been previously treated with imatinib mesylate and sunitinib malate. It is supplied as a tablet for oral administration. The recommended dose is 160 mg (four 40 mg tablets) taken orally once daily for the first 21 days of each 28 day cycle. Continue treatment until disease progression or unacceptable toxicity. It should swallow whole and taken with a low-fat breakfast.

#### 1.4. Mechanism of Action

Stivarga (regorafenib) is a potent oral multi-kinase inhibitor with a kinase inhibition profile targeting angiogenic, stromal and oncogenic receptor tyrosine kinases (TK). This distinct anti-angiogenic profile includes inhibition of both VEGFR2 and TIE2 TK.

#### 1.5. Side Effects

Adverse events associated with the use of Stivarga for GIST include: asthenia/fatigue, HFSR, diarrhea, decreased appetite/food intake, hypertension, mucositis, dysphonia, infection, pain, decreased weight, gastrointestinal and abdominal pain, rash, fever, nausea.

### 2. RAVICTI (GLYCEROL PHENYLBUTYRATE)

#### 2.1. Company

Hyperion Therapeutics; Approved by February 2013.

#### 2.2. Treatment Area

Pediatrics and adults with urea cycle disorders

#### 2.3. General Information

Ravicti (glycerol phenylbutyrate) is a nitrogen-binding agent. Urea cycle disorders result from deficiencies in the enzymes responsible for clearing toxic ammonia from the blood. During protein metabolism, nitrogen is produced as a waste product, which is normally converted to urea and excreted. In patients with urea cycle disorders, the nitrogen accumulates as ammonia and can cause coma, brain damage, and death. Glycerol phenylbutyrate aids in the removal of this accumulated ammonia. Ravicti is specifically indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients over 2 years of age with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. It is supplied as a liquid for oral administration. It should be taken with food and administered directly into the mouth via oral syringe or dosing cup. The maximum total daily dosage is 17.5 mL (19 g).

#### 2.4. Mechanism of Action

Ravicti (glycerol phenylbutyrate) is a nitrogen-binding agent. UCDs are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia (NH<sub>3</sub>, NH<sub>4</sub><sup>+</sup>). Absence of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected patients. Ravicti is a triglyceride containing 3 molecules of phenylbutyrate (PBA). PAA, the major metabolite of PBA, is the active moiety of Ravicti. PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form PAGN, which is excreted by the kidneys. On a molar basis, PAGN, like urea, contains 2 moles of nitrogen and provides an alternate vehicle for waste nitrogen excretion.

#### 2.5. Side Effects

Adverse events associated with the use of Ravicti include: diarrhea, flatulence, headache.

### 3. POMALYST (POMALIDOMIDE)

#### 3.1. Company

Celgene; Approved by February 2013

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Drug discovery, 2013, 4(10), 5-6,

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### 3.2. Treatment Area

Relapsed and refractory multiple myeloma

### 3.3. General Information

Pomalyst (pomalidomide) is an immunomodulatory antineoplastic agent. It is specifically indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. It is supplied as a capsule for oral administration. The recommended starting dose is 4 mg once daily orally on Days 1-21 of repeated 28-day cycles until disease progression. It should be taken without food (at least 2 hours before or 2 hours after a meal). It may be given in combination with dexamethasone.

### 3.4. Mechanism of Action

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In in-vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer cell-mediated immunity and inhibit the production of pro-inflammatory cytokines by monocytes.

### 3.5. Side Effects

Adverse events associated with the use of Pomalyst include: fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper-respiratory tract infections, back pain, pyrexia.

## 4. KADCYLA (ADO-TRASTUZUMAB EMTANSINE)

### 4.1. Company

Genentech; Approved by February 2013

### 4.2. Treatment Area

HER2-positive metastatic breast cancer

### 4.3. General Information

Kadcyla is specifically indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. It is supplied as a solution designed for intravenous infusion. The recommended initial dose is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Do not administer Kadcyla at doses greater than 3.6 mg/kg. First infusion: Administer infusion over 90 minutes. Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion related reactions. Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated. Patients should be observed during the infusion and for at least 30 minutes after infusion.

### 4.4. Mechanism of Action

Ado-trastuzumab emtansine is a HER2-targeted antibody-drug conjugate. The antibody is the humanized anti-HER2 IgG1, trastuzumab. The small molecule cytotoxin, DM1, is a microtubule inhibitor. Upon binding to sub-domain IV of the HER2 receptor, ado-trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, which results in cell cycle arrest and apoptotic cell death.

### 4.5. Side Effects

Adverse events associated with the use of Kadcyla include: fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation.